Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The FHN Trial Group. In-center hemodialysis six times per week versus three times per week. N Engl J Med 2010;363:2287-300. DOI: 10.1056/NEJMoa1001593.

Appendix 1

List of institutions and investigators in the FHN Daily Trial Group

FHN Daily Trial Group

Chair, Steering Committee: Kliger A; NIDDK: Eggers P, Briggs J, Hostetter T, Narva A, Star R; Centers for Medicare and Medical Services: Augustine B, Mohr P; Data Coordinating Center – Cleveland Clinic: Beck G (PI), Fu Z, Gassman J, Greene T, Daugirdas J, Hunsicker L, Larive B, Li M, MacKrell J, Wiggins K, Sherer S, Weiss B; Central MRI Core – The Ohio State University Medical Center and Mt. Sinai Medical Center: Rajagopalan S, Sanz J, Dellagrottaglie S, Kariisa M; Tran T, West J; Central Quality of Life Core – University of Pittsburgh: Unruh M; Beach S, Keene R, Schlarb J; Central Holter Core– Toronto General Hospital: Chan C; McGrath-Chong M; Biospecimen Repository – Fisher BioServices: Frome R, Higgins H, Ke S, Mandaci O, Snell C; Data Safety and Monitoring Board: Eknoyan G (Chair), Appel L, Cheung A, Derse A, Kramer C, Geller N, Grimm R, Henderson L, Prichard S, Roecker E; **Daily Trial Clinical Sites** – University of California San Francisco (UCSF)/Stanford Consortium: Chertow G (PI); UCSF and San Francisco Bay Area: James S, Chertow G, Tamura M, Hall Y, McCulloch C, Painter P, Gorodetskaya I, Tichy M, Humphreys M, Luan J, Escalada R, Rodriquez R; UC Davis and Sacramento Area: Depner T, Kaysen G, Suter M, Sonico J, Anderson S; El Camino Hospital and Satellite Health Care: Ting G, Schiller-Moran B, Coplon N, Doss S, Rogers J, Dominguez A, Atwal J, Lemus D; UCLA and Los Angeles Area: Rastogi A, Nissenson A, Goodman W, Salusky I, Schweitzer S, Rivas M, Smith M, Gayda P, Hernandez A, Rashid M; UCSD and San Diego Area: Mehta R, Pepas J, Bharti B, Nabali A, Manaster R, Mathew R, Shah S, Sanz G, Wei J; University of Texas, San Antonio: Ayus J, Achinger S, Gutierrez M; Renal Research Institute (RRI) New York Consortium: Levin N (PI); Bay W, Carter M, Geronemus R, Kuhlmann M, Handelman G, Gotch F, Finkelstein F, Kimmel P, Lacson E, Ornt D, Greenwood R, Vassalotti J, Burrowes J; RRI New York City: Levin N, Kotanko P, Kaufman A, Winchester J, Meisels I, Chang J, Fofie Y, Ramos R, Sergeyeva O, Callegari J, Arthur B, Tarallo M, Ulloa D, Apruzzes R; University of Western Ontario: Lindsay R, Suri R, Garg A, Bullas R Mazzorato A; Wake Forest University School of Medicine: Rocco M, Burkart J, Moossavi S, Mauck V, Kaufman T, Coppley A; Vanderbilt University Medical Center: Schulman G, McLeroy S, Sika M, Leavell E; Barnes Jewish/Washington University: Miller B, Schussler R, Bardsley J, Skelton R.

Appendix 2. Participating Dialysis Sites

Dialysis Unit	Location
Southern Manhattan Dialysis Center	New York, NY
Queens Artificial Kidney Center	Jackson Heights, NY
South Queens Dialysis Center	Jamaica, NY
Yorkville Dialysis Center	New York, NY
Irving Place Dialysis Center	New York, NY
Upper Manhattan Dialysis Center	New York, NY
Mt. Sinai - 94th Street HD Unit	New York, NY
St. Albans Dialysis Center	Jamaica, NY
LHSC - WC (Westminster Campus)	London, Ontario
LHSC - SSC (South Street Campus)	London, Ontario
UC (University Campus)	London, Ontario
LHSC - LS (London Satellite)	London, Ontario
Lexington Dialysis Center	Lexington, NC
Piedmont Dialysis Center	Winston Salem, NC
Salem Kidney Center	Winston Salem, NC
West Iredell Dialysis Center	Statesville, NC
Vanderbilt Dialysis Clinic	Nashville, TN
Chromalloy American Kidney Center	St. Louis, MO
Barnes-Jewish	St. Louis, MO
UCSF-Mt. Zion (adult)	San Francisco, CA
San Francisco General Hospital (SFGH)	San Francisco, CA
RAI Ocean	San Francisco, CA
DaVita San Francisco	San Francisco, CA
DaVita Chinatown	San Francisco, CA
DaVita Walnut Creek	Walnut Creek, CA
Mills Peninsula Dialysis Clinic	San Mateo, CA
Burlingame Dialysis Center	Burlingame, CA
RAI Cesar Chavez	San Francisco, CA
DaVita Concord	Concord, CA
DaVita South Hayward	Hayward, CA
DaVita Hayward	Hayward, CA
DCI University	Sacramento, CA
DCI Southgate	Sacramento, CA
DCI Madison	Sacramento, CA
RAI Elk Grove	Elk Grove, CA
DaVita Alhambra	Sacramento, CA
El Camino Hospital	Mountain View, CA
El Camino Evergreen	San Jose, CA
Satellite San Jose (East)	San Jose, CA
Satellite San Jose (West)	San Jose, CA
Satellite Gilroy	Gilroy, CA
Satellite Larkspur	Greenbrae, CA
Satellite Santa Rosa	Santa Rosa, CA
Satellite Dialysis South San Francisco	San Francisco, CA
UCLA Medical Center (adult)	Los Angeles, CA
UCLA Medical Center (pediatrics)	Los Angeles, CA
DaVita Hollywood Dialysis Center	Los Angeles, CA

South Valley Regional Dialysis Center	Encino, CA
DaVita USC Kidney Center	Los Angeles, CA
UCSD Medical Center (adult)	San Diego, CA
DaVita-Chula Vista	Chula Vista, CA
DaVita-Gateway	San Diego, CA
DaVita-San Ysidro	San Diego, CA
RAI El Cajon	El Cajon, CA
Kearny Mesa Dialysis Center	San Diego, CA
RAI Broadway-Chula Vista	Chula Vista, CA
University Hospital Dialysis West	San Antonio, TX

Methods Supplement - Statistical Analyses of Quantitative Secondary Outcomes

We performed analyses of quantitative secondary outcomes on observed data without imputation of missing values by applying mixed effects analyses using an unstructured covariance model to account for correlations in measurements over time, with covariate adjustment for age, diabetes, clinical center and the baseline variable under analysis. Statistical inference was performed using restricted maximum likelihood. These models were used to compare mean changes from baseline to 12 months between treatment groups while incorporating data at baseline, 4 months, and 12 months for each quantitative outcome except LVM, for which only baseline and 12-month measurements were obtained. We incorporated average values from months 3–5 and 10–12 for analyses of change in serum albumin, phosphorus, hemoglobin, and the weekly average pre-dialysis systolic blood pressure. Because the mixed models included the month 4 data, early changes in outcomes to 4 months were incorporated in the analyses of means changes to 12 months for patients who dropped out of the study between month 4 and month 12 or who remained in the study but missed their month 12 measurement.

This mixed effects analysis was used for all of the quantitative outcomes described in Table 3 with the exception of the Trail Making B, for which approximately 25% of patients failed to complete the test, and the number of antihyptertensive agents, which followed a discrete distribution. The 12-month values of these two factors were compared between the treatment groups using an exact stratified Wilcoxon rank sums test (failure to complete the Trail Making B was assigned the least favorable rank), with stratification for quartile of the baseline value of the factor being analyzed.

Methods Supplement – Study Design, Data Acquisition and Analysis, and Manuscript Writing

The FHN Daily Trial was designed by the Steering Committee of the FHN Trials. Dr. Chertow and Dr. Levin are Principal Investigators of the two clinical consortia for the Daily Trial. The final trial design incorporated elements of both initial proposals, along with input from site Investigators and other experts. Data were gathered by Study Coordinators based at each clinical site, directed by two lead Study Coordinators (Dr. Sergeyeva and Ms. Gorodetskaya). Data were managed and analyzed by Investigators and staff at the Data Coordinating Center (DCC) at Cleveland Clinic Foundation (Dr. Gerald Beck, Principal Investigator). The DCC and Investigators vouch for the data and analysis. Dr. Chertow wrote the first draft of the manuscript and coordinated editing, dissemination and submission of all versions of the manuscript including the final version submitted. Only study personnel who signed a confidentiality agreement with the DCC were allowed to view preliminary analyses, shared at a Steering Committee meeting in Bethesda, MD on July 13-14, 2010. All personnel pledged to keep the Daily Trial results confidential during the period of embargo.

Supplement Table 1. FHN Daily Trial Eligibility Criteria

Inclusion Criteria

- Patients with end-stage renal disease requiring chronic renal replacement therapy
- Age $\geq$ 13 years
- Achieved mean eKt/V $\geq$ 1.0 for last two baseline hemodialysis sessions
- Weight $\geq$ 30 kg

Exclusion Criteria

- Unable or unwilling to follow the study protocol for any reason (including mental incompetence)
- Unable or unwilling to provide informed consent or sign the Institutional Review Board-approved consent form
- Requires HD >3 times per week due to medical comorbidity (such as, but not limited to: systemic oxalosis or requiring total parenteral nutrition). Occasional ultrafiltration on a fourth day per week is not an exclusion criterion.
- Current pregnancy, or actively planning to become pregnant in the next 12 months
- History of poor adherence thrice weekly HD
- Inability to come for in-center HD 6 days per week, including inability to arrange adequate transportation
- Expected geographic unavailability at a participating HD unit for >2 consecutive weeks or >4 weeks total during the next 14 months (excluding unavailability due to hospitalizations)
- Currently in an acute or chronic care hospital
- Contraindication to heparin, including allergy or heparin induced thrombocytopenia
- Expectation that native kidneys will recover
- Residual renal clearance >3ml/min per 35 L
- Currently on daily or nocturnal HD or less than 3 months since the subject discontinued daily or nocturnal HD
- Less than 3 months since patient returned to HD after acute rejection resulting in allograft failure
- Current use of investigational drugs or participation in another clinical trial that contradicts or interferes with the therapies or measured outcomes in this trial
- Scheduled for living donor kidney transplant, change to peritoneal dialysis, or plans to relocate to a non-study center within the next 14 months
- Life expectancy less than 6 months
- Medical history that might limit the patient's ability to take the trial treatments and complete the 12 month duration of the study, including: currently receiving chemo or radiotherapy for a malignant neoplastic disease other than localized non-melanoma skin cancer, active systemic infection (including tuberculosis, disseminated fungal infection, active AIDS but not HIV), and cirrhosis with encephalopathy
- Medical conditions that would prevent the subject from performing the cardiac MRI procedure (e.g., inability to remain still for the procedure, a metallic object in the body, including cardiac pacemaker, inner ear (cochlear) implant, brain aneurysm clips, mechanical heart valves, recently placed artificial joints, and older vascular stents)
- Inability to communicate verbally in English or Spanish
- Vascular access being used for HD is a non-tunneled catheter

SUPPLEMENT FIGURE LEGENDS:

Supplement Figure 1: FHN Daily Trial Patient Flow

Supplement Figure 2: Separation in Treatment Parameters between Groups

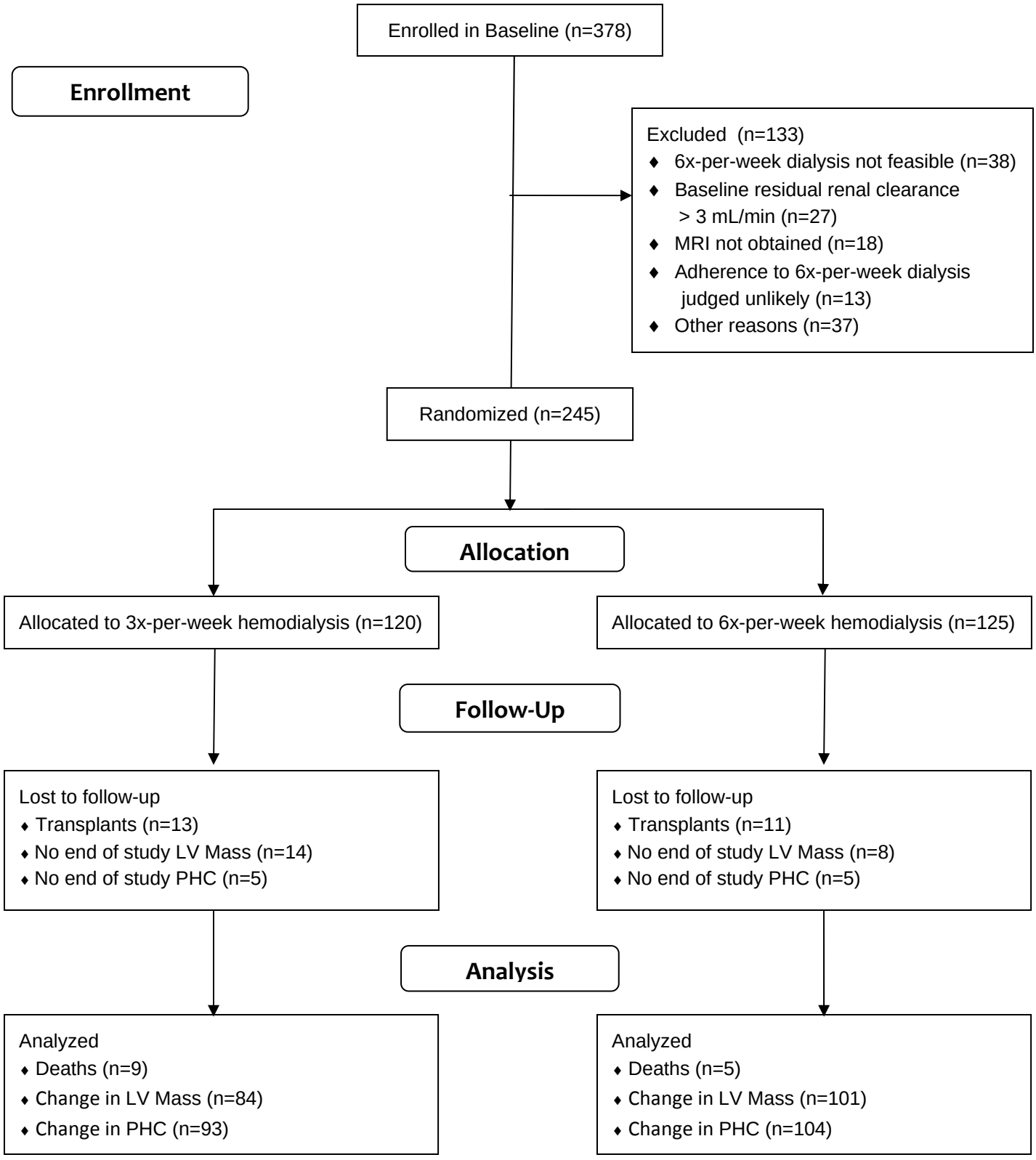
Shown are distributions of the number of dialysis treatments per week (left), weekly treatment time in hours (center), and weekly standard Kt/V_{urea} (right) for the 3 times per week (top) and 6 times per week (bottom) treatment groups. Each quantity was first averaged over the follow-up period separately for each patient. See Table 2 for means and standard deviations. 119 patients were included in the summaries of each of the three parameters for the 3 times per week group, and 125, 125, and 124 were included in the summaries of the number of treatments per week, weekly treatment time, and weekly standard Kt/V_{urea} in the 6 times per week group.

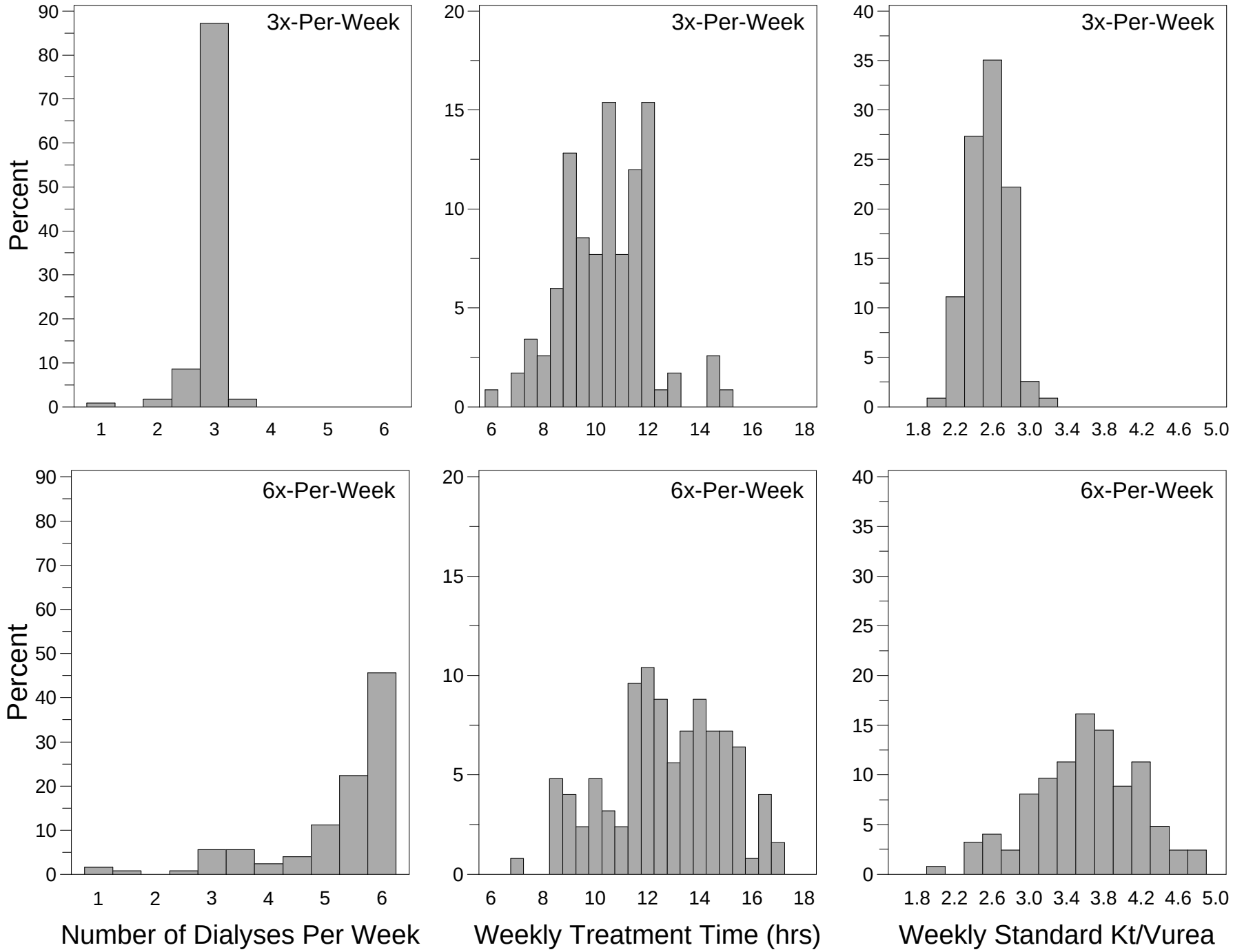
Supplement Figure 3: Histogram of Change in LVM and PHC

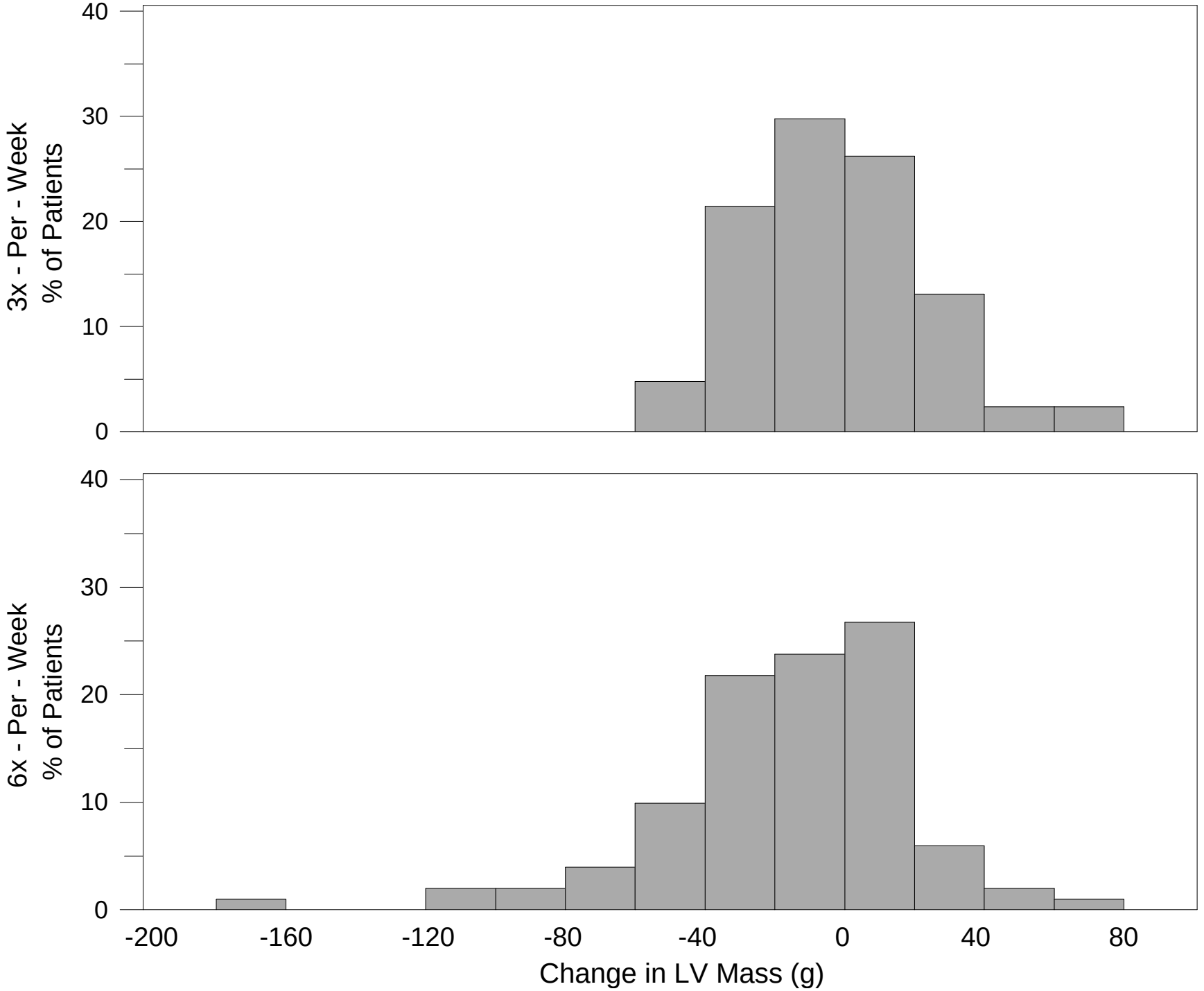
Shown are distributions of the change in LVM (n=199) and PHC (n=211) in the 3 times per week and 6 times per week groups.

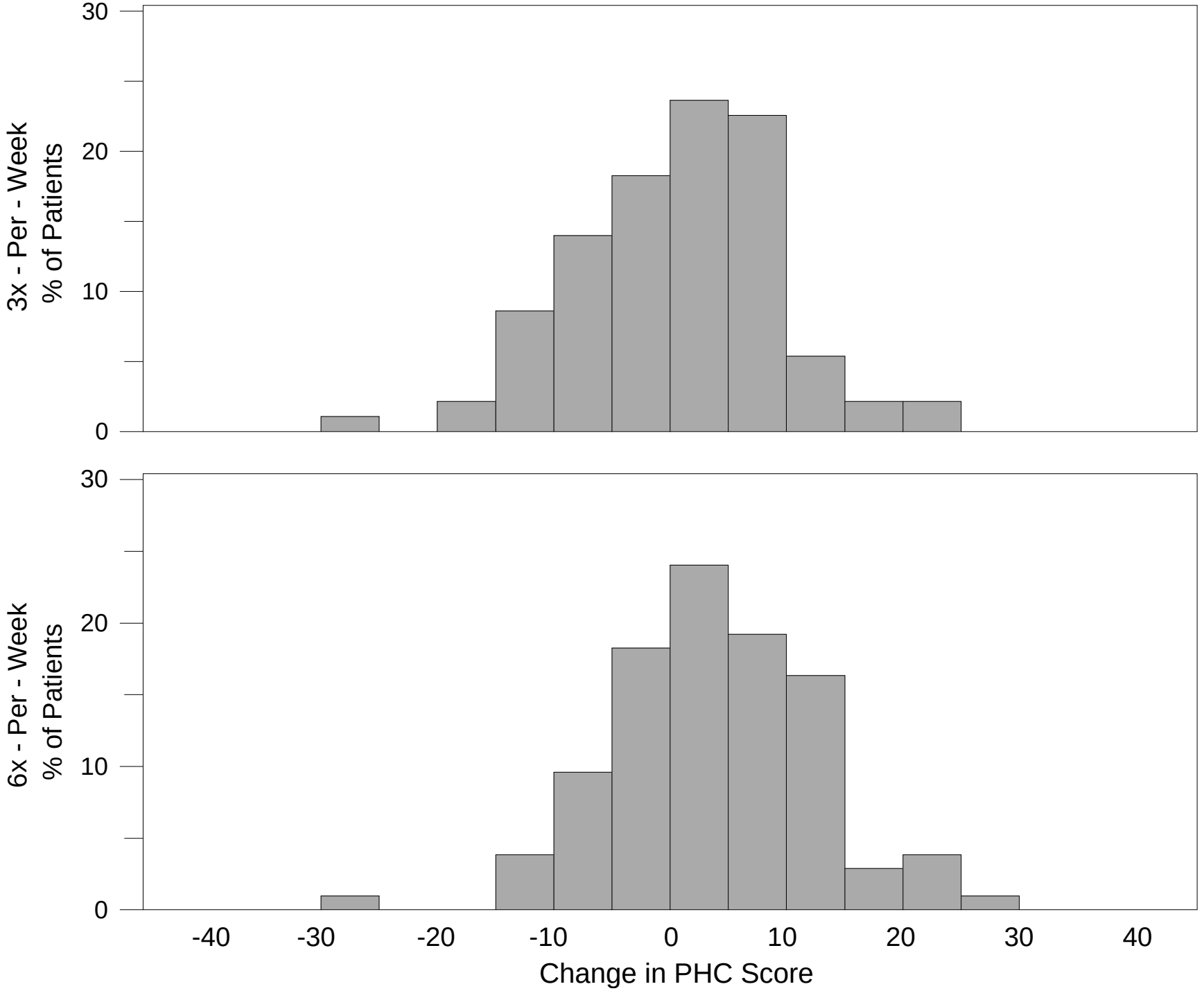
Supplement Figure 4: Time to First Vascular Access Intervention

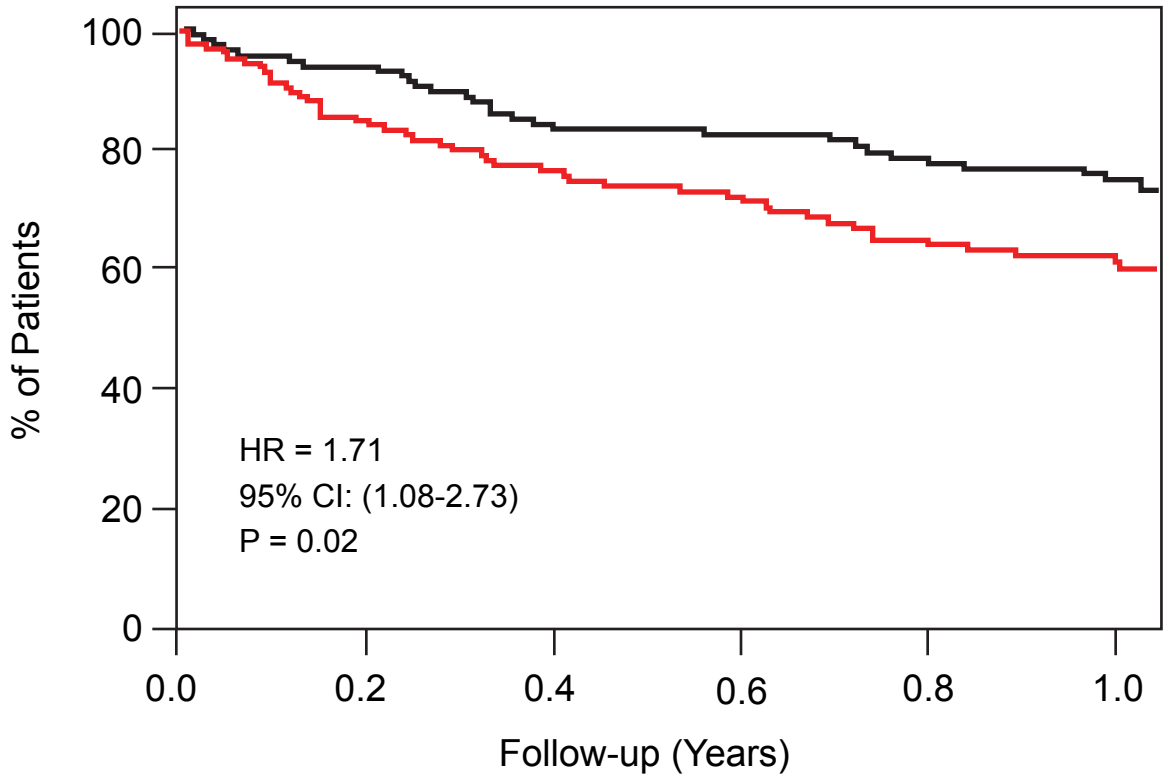
Shown are Kaplan-Meier curves in the 3 times per week (black) and 6 times per week (red) groups for the time from randomization to each patient's first access event. The hazard ratio was computed by Cox regression, with adjustment for diabetes, age, and clinical center. In months 0-3, 3-6, 6-9 and 9-12, there were 38, 19, 21 and 17 interventions in the 6 times per week arm and 20, 17, 12 and 16 in the 3 times per week arm, respectively.


Enrollment
Enrolled in Baseline (n=378)
Excluded (n=133)
♦ 6x-per-week dialysis not feasible (n=38)
♦ Baseline residual renal clearance > 3 mL/min (n=27)
♦ MRI not obtained (n=18)
♦ Adherence to 6x-per-week dialysis judged unlikely (n=13)
♦ Other reasons (n=37)
Randomized (n=245)
Allocation
Allocated to 3x-per-week hemodialysis (n=120)
Allocated to 6x-per-week hemodialysis (n=125)
Follow-Up
Lost to follow-up
♦ Transplants (n=13)
♦ No end of study LV Mass (n=14)
♦ No end of study PHC (n=5)
Lost to follow-up
♦ Transplants (n=11)
♦ No end of study LV Mass (n=8)
♦ No end of study PHC (n=5)
Analysis
Analyzed
♦ Deaths (n=9)
♦ Change in LV Mass (n=84)
♦ Change in PHC (n=93)
Analyzed
♦ Deaths (n=5)
♦ Change in LV Mass (n=101)
♦ Change in PHC (n=104)


3x-Per-Week
3x-Per-Week
3x-Per-Week
6x-Per-Week
6x-Per-Week
6x-Per-Week
Percent
Percent
Number of Dialyses Per Week
Weekly Treatment Time (hrs)
Weekly Standard Kt/Vurea


3x - Per - Week
% of Patients
40
30
20
10
0
6x - Per - Week
% of Patients
40
30
20
10
0
-200
-160
-120
-80
-40
0
40
80
Change in LV Mass (g)


3x - Per - Week
% of Patients
30
20
10
0
6x - Per - Week
% of Patients
30
20
10
0
-40
-30
-20
-10
0
10
20
30
40
Change in PHC Score


100
80
60
40
20
0
% of Patients
HR = 1.71
95% CI: (1.08-2.73)
P = 0.02
0.0
0.2
0.4
0.6
0.8
1.0
Follow-up (Years)